Photoselective vaporization of the prostate: study outcomes as a function of risk of bias, conflicts of interest, and industrial sponsorship

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Abstract: PURPOSE To investigate the outcomes of comparative studies on photoselective vaporization of the prostate (PVP) as a function of risk of bias (RoB), conflicts of interest (COI), and industrial sponsorship (IS). METHODS We performed a systematic literature search for comparative studies on PVP [randomized controlled trials (RCTs) and non-randomized comparative studies (NRCSs)]. Study selection as well as comprehensive assessment of RoB, COIs, and IS were performed in duplicate. The identified studies were further rated by two independent board-certified urologists as either PVP-favourable or PVP-unfavourable. Descriptive statistics were performed among all identified studies and among the subgroups of studies rated as favourable and unfavourable, respectively. RESULTS Sixty-five studies qualified for inclusion (25 RTCs and 40 NRCSs) of which 56 (86%) were rated favourable and 9 (14%) unfavourable. A majority of all studies mentioned the absence/presence of potential COIs (78%). In contrast, a sponsorship statement was only found in 29% of the investigations. Studies rated favourable demonstrated a higher percentage of COIs (39% versus 22%). IS was exclusively found among favourable studies. Furthermore, a serious or critical RoB was more often found in favourably rated NRCSs. CONCLUSIONS COIs and IS seem to be associated with favourable study outcomes in comparative studies on PVP. The transparency of the whole research process from study conception to the dissemination of the results has to be further improved to prevent a harmful effect of COIs and IS on the internal validity of studies.

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Abstract

Purpose: To investigate the outcomes of comparative studies on photoselective vaporization of the prostate (PVP) as a function of risk of bias (RoB), conflicts of interest (COI) and industrial sponsorship (IS).

Methods: We performed a systematic literature search for comparative studies on PVP (randomized controlled trials [RCTs], non-randomized comparative studies [NRCSs]). Study selection as well as comprehensive assessment of RoB, COIs and IS were performed in duplicate. The identified studies were further rated by two independent board-certified urologists as either PVP-favourable or PVP-unfavourable. Descriptive statistics were performed among all identified studies and among the subgroups of studies rated as favourable and unfavourable, respectively.

Results: Sixty-five studies qualified for inclusion (25 RTCs, 40 NRCSs) of which 56 (86%) were rated favourable and 9 (14%) unfavourable. A majority of all studies mentioned the absence/presence of potential COIs (78%). In contrast, a sponsorship statement was only found in 29% of the investigations. Studies rated favourable demonstrated a higher percentage of COIs (39% vs. 22%). IS was exclusively found among favourable studies. Furthermore, a serious or critical RoB was more often found in favourably rated NRCSs.

Conclusions: COIs and IS seem to be associated with favourable study outcomes in comparative studies on PVP. The transparency of the whole research process from study conception to the dissemination of the results has to be further improved to prevent a harmful effect of COIs and IS on the internal validity of studies.

Introduction

Photoselective vaporization of the prostate (PVP), also known as Greenlight laser vaporization, is a surgical treatment option for non-neurogenic lower urinary tract symptoms secondary to prostate enlargement. A randomized controlled trial (RCT) comparing the gold-standard treatment (transurethral resection of the prostate; TURP) with PVP demonstrated non-inferiority of PVP regarding functional (International Prostate Symptom Score, maximum flow rate) and safety outcomes (freedom from complications) [1,2]. The trial also revealed that PVP was in favour in terms of catheterization time, length of hospital stay and surgical re-intervention within 30 days after the procedure [3]. In addition, several studies investigated the beneficial hemostatic properties of the laser system which allow a safe operation in patients taking anticoagulants [4–6]. As PVP offers comparable functional results at a lower morbidity, it can be considered a major competitor to TURP.

Conflicts of interest (COI) and industrial sponsorship (IS) can impact the internal and external validity of studies by introducing various types of bias leading to a distortion of the clinical decision-making process. It has been shown that studies involving COIs and/or IS more often report favourable outcomes [7,8]. Prostatic obstruction syndrome is a highly prevalent disease for which numerous competing surgical and non-surgical treatment options exist. Although PVP is a major competitor at this market, the interaction between PVP-specific study outcomes, risk of bias (RoB), COI and IS has never been investigated so far. Hence, the aim of the present investigation was to evaluate the outcomes of comparative PVP studies as a function of RoB, COI and IS.

Materials and methods

Search strategy and selection of studies

A systematic literature search involving the MEDLINE (Ovid SP) and EMBASE (Ovid SP) databases was conducted on August 22, 2017. The search strategy is presented in *Online Resource 1*. Study selection and data abstraction was carried out in duplicate by a team of 3 reviewers (M.S.W., C.P., A.S.N). Disagreements between the reviewers were resolved by discussion. After deduplication, title/abstract screening and full-text analysis were performed to select articles in English language that involved PVP studies using either the 80W potassium titanyl phosphate (KTP), the 120W lithium triborate (LBO) and/or the 180W LBO laser system. Eligible study designs were randomized controlled trials (RCTs) and non-randomized comparative studies (NRCSs), in which a PVP system was either compared to an alternative surgical treatment option (e.g. 180W LBO versus TURP) or to another PVP system (e.g. 180W LBO versus 120W LBO). Studies that involved bench research, animals, cadavers or experimental laser systems were excluded. Furthermore, studies investigating photoselective vaporization to other pathologies than prostatic obstruction were considered ineligible. Systematic reviews/meta-analyses, narrative reviews, commentaries, editorials, letters, case reports, study protocols, abstracts and book chapters were also excluded.

Data abstraction and assessment of risk of bias

For each included study we abstracted (1) design, (2) PVP system, (3) comparator, (4) primary endpoint, (5) geographic region of the study and (6) journal including impact factor (IF; abstracted according to Thomson Reuters Journal Citation Reports 2018 [9]). The RoB of the identified RCTs and NRCSs was evaluated by The Cochrane Collaboration's tool for assessing RoB [10] and the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool [11], respectively. The first tool assesses seven criteria and assigns the judgments low/high/unclear RoB to each criterion while the second tool is structured around

seven domains of bias that are separately graded as low/moderate/serious/critical RoB. Furthermore, the NRCSs were evaluated regarding their temporality (prospective versus retrospective) including determination of the prospective components.

Assessment of conflicts of interest and industrial sponsorship

Each study was assessed regarding the presence of a COI statement. If a COI statement was present, we distinguished between "no COI declared" (absence of COIs) and "COI declared" (presence of at least one COI). Furthermore, a recursive search mechanism was applied to identify additional non-declared COIs: First, we established a database of all authors for which a COI was declared (conflicted authors). Second, the author lists of all studies without a COI statement or without the declaration of COIs were re-evaluated for the presence of conflicted authors. In the presence of a least one conflicted author we mutated the COI assessment of the corresponding study to "COI declared". After identification of sponsorship statements, a differentiation between "no sponsorship declared" and "sponsorship declared" was made. For studies rated as "sponsorship declared" we further stratified by the type of sponsorship (public, industrial, institutional or private funding). Assessment of RoB, COI and IS was performed in duplicate by a team of 3 reviewers (M.S.W., C.P., A.S.N) and disagreements were resolved by discussion.

Assessment of favourability of study outcomes

Two board certified urologists (D.T.S.W, J.O.H) that were not involved in the study selection, data abstraction and evaluation of RoB, COI or IS, independently assessed the favourability of the study outcomes. A third board certified urologist (T.H) was consulted in the event of disagreement. The assessors rated the studies either as favourable (superior or non-inferior PVP results) or unfavourable (inferior PVP results). In comparisons between PVP systems (e.g. 180W LBO versus 120W LBO), the assessors assigned the judgment "favourable" to studies in which the results of the newer laser system were superior to the older one and the

judgment “unfavourable” to studies in which the results of the newer laser system were inferior or non-inferior to the older one. The abstracted data was analyzed using SPSS Version 24 (IBM Corp., Armonk, NY, USA). All descriptive statistics were first performed among the whole study collective and second among the strata “favourable” and “unfavourable”.

Results

The study selection process is demonstrated in *Fig. 1*. After manual deduplication, titles and abstracts of 749 records were screened rendering 286 articles eligible for full text analysis. Ultimately, 65 articles (25 RCTs [38%] and 40 NRCSs [62%]) qualified for inclusion.

Characteristics of included studies

Study characteristics are presented in *Online Resource 2*. Nineteen (29%) studies investigated the 80W KTP system, 25 (38%) the 120W LBO system, 6 (9%) the 180W LBO system and 9 (14%) combinations of the aforementioned systems. The exact laser model used was not identifiable in 6 (10%) studies. More than half of all studies compared PVP to TURP (N=42, 65%). The second most common comparator was the holmium laser (N=14, 22%). Six (9%) studies compared different PVP systems (e.g. 180W LBO versus 120W LBO). Comparisons with the diode laser (N= 3, 5%), thulium laser (N=2, 3%), open prostatectomy (N=2, 3%) and transurethral electrovaporization (N=1, 2%) were rare.

Most studies reported urinary function as a primary endpoint (N=40, 62%). Six (9%) studies primarily reported on economical outcomes while 5 (8%) and 2 (3%) studies considered safety and sexual function as primary endpoints, respectively. Twelve (18%) investigations did not define a primary endpoint and/or reported on another type of primary endpoint (e.g. intraoperative production of harmful gases by tissue ablation). Thirty-five percent of the studies were performed in Europe followed by Asia (32%), North America (23%), Australia (8%) and South America (2%). The 65 included studies were published in 23 different journals. The outcomes of 56 (86%) of the identified 65 studies were rated as favourable while 9 (14%) study outcomes were regarded as unfavourable. Favourable study outcomes were more common in RCTs than in NRCSs (24/25 [96%] versus 32/40 [80%]).

Risk of bias

The results of the overall RoB assessment are summarized in *Online Resource 3* (RCTs) and *Online Resource 4* (NRCSs). The overall evaluation of the RCTs was impeded by the relative dominance of the rating category "unclear RoB" while the stratified analysis (*Online Resource 5*, strata: favourability of study outcomes) was additionally limited by the low number of RCTs rated as unfavourable (N=1). Of all NRCSs, 20 (50%) were rated as prospective and 50 (50%) as retrospective. The correct determination of the prospective components was often impeded by imprecise and/or inconsistent manuscript wording. The domain "confounding" was rated in 65% of the identified NRCSs as either "serious RoB" or "critical RoB". The stratified RoB assessment (*Online Resource 5*) demonstrated a relatively higher occurrence of the judgements "serious/critical RoB" among the NRCSs rated as favourable compared to the ones rated as unfavourable (confounding: 69% versus 50%, deviation from intended interventions: 3% versus 0%, missing data: 22% versus 0%, outcome measurement: 66% versus 50%).

Conflicts of interest and industrial sponsorship

The results of the assessment of COIs and IS are presented in *Online Resource 6*. A majority of the identified studies had a COI statement (N=51, 78%). In 24 (37%) studies at least one COI was declared. In total, 56 critical authors with COIs were identified. One study declared 18 authors with COIs (median per study: 2.33). The recursive search strategy yielded 6 studies with 36 additional undeclared COIs (study 1: 16 undeclared COIs, study 2: 16 undeclared COIs, studies 3 to 6: one undeclared COI per study). Three (50%) of these 6 studies were RCTs. In contrast, a sponsorship statement was only present in about one third of all studies (N=19, 29%). These statements denied any sponsorship in 8 studies (12%) and declared public, industrial and institutional sponsorship in 5 (8%), 4 (6%) and 2 (3%) studies,

respectively. Of the four industry-sponsored studies, 3 (75%) were RCTs and one (25%) was a NRCS.

Fig. 2 illustrates the favourability of the study outcomes as a function of the COI and IS assessment. The presence of COI statements was indifferent to the favourability of the study outcomes (favourable: 79%, unfavourable: 78%). However, studies rated as favourable had more often at least one COI (39% versus 22%). The mean number of COIs was 0.93 in favourable and 0.44 in unfavourable studies. Moreover, the 6 studies for which our recursive search mechanism yielded a total of 36 additional non-declared COIs were all rated as favourable. The presence of sponsorship statements was comparable between favourable and unfavourable studies (29% versus 33%). However, favourable studies more often received financial support (7% versus 0%). Furthermore, none of the industry-sponsored studies (N=4) were rated as unfavourable.

Discussion

To the best of our knowledge this is the first study comprehensively investigating the interaction between study outcomes, RoB, COI and IS in the field of comparative PVP literature. Prostatic obstruction syndrome is a highly prevalent disease for which numerous competing surgical and non-surgical treatment options exist. The perception of comparative PVP study results within the urologic community is thus crucial from an economical perspective, not only for the involved industry itself but also for surgeons, institutions and health care systems offering this treatment modality to their patients. Of all 65 identified studies, 56 (86%) were rated as favourable and 9 (14%) as unfavourable. Within the group of NRCSs, the RoB judgments “serious RoB” and “critical RoB” were more common in studies rated as favourable. Among RCTs, the RoB assessment was hampered by low quantity and quality of reporting. Therefore, a valid conclusion could not be draw. Statements regarding COIs and sponsorship were found in about 80% and 30% of all identified studies, respectively. COIs, overall sponsorship and IS were apparently more common in studies rated as favourable.

Similar research in the field of urology was performed by *Schoenthaler et al.* [12] and *Boscolo-Berto et al.* [13]. The first investigation evaluated level of evidence, sponsorship, COI policy and commercial impact of MEDLINE-listed clinical urolithiasis-related trials. Although the study team detected a comparable proportion of COI statements (90%), sponsorship statements (33%) and IS (5%), only 6% of their identified studies were afflicted by COIs compared to 37% in our investigation. The authors of the second study performed a SCOPUS literature search for publications on the efficacy/safety of phosphodiesterase inhibitors to treat erectile dysfunction. They concluded by multivariable logistic regression that the total number of financial COIs was the strongest predictor for a favourable rating of the study outcome. Numerous investigations outside the field of urology did also demonstrate

a higher occurrence of pro-industry outcomes in studies afflicted by COIs [7] and IS [8,14–18]. Furthermore, prior literature revealed associations between the presence of COIs/IS and lower quality of research [19,20], lower likelihood of publication [21,22] and delayed publication [23]. A possible explanation of the latter two findings is a sponsor-driven interest not to publish unfavourable study outcomes.

Clinician-scientists actively engaging with the industry are important drivers of innovation and financial support through industrial sponsorship is often required to launch a sufficiently powered study, especially in the setting of an already established comparator such as TURP. This leads inevitably to a relationship of dependence between the investigator and the sponsor. Particularly in the setting of unfavourable results, the sponsor might be tempted to influence the investigator regarding the implementation, data analysis and publication of the study [24]. Therefore, the relationship between the sponsor and the investigator has to be fully disclosed at several levels. First, detailed COI and IS statements defining the exact role of the sponsor have to be strictly enforced by journal editors. Second, reporting of COIs and IS should ideally already occur before the actual initiation of the study in the format of preregistered protocols. Third and last, overall reporting of methodology and results should be further enhanced (RCTs: CONSORT [25], NRCS: STROBE [26]) as all studies are at potential RoB regardless of the presence/absence of COIs and/or IS.

Our investigation has several strengths: We used a methodologically rigorous approach regarding literature search and study selection as known from systematic reviews. Furthermore, RoB assessment was performed using two well-established instruments. Additionally, the rating of the favourability of the study outcomes was conducted by a team of reviewers that independently rated the included studies and were not involved in the systematic literature search, study selection and evaluation of RoB/COIs/IS to guarantee an

unbiased assessment. Finally, the risk of underreporting of COIs was partially mitigated by our recursive search mechanism, which identified additional 36 COIs in a total of 6 studies.

However, this study is not without limitations. The assessment of RoB, COIs and IS was fully dependent on the quality and the quantity of reporting. Therefore, especially among the identified RCTs, the frequency of studies rated as “high RoB” might be underestimated in the light of the relative dominance of the judgment “unclear RoB”. Furthermore, our recursive search mechanism did not account for hypothetical temporal dynamics of COIs. For example, a researcher having a COI in the year 2012 might not have a COI anymore in 2014. Moreover, the number of identified studies did not allow for a meaningful time series or multivariable regression analysis. Such approaches would have the potential to detect temporal trends in reporting of COI/IS statements or to identify independent predictors of favourable study outcomes. Last, our work mainly focused on financial COIs, although the concept of COI can involve many more dimensions. Researchers might, for example, also be conflicted due to personal preferences or due to their academic activities.

COIs and IS seem to be associated with favourable study outcomes in comparative studies on PVP. Surprisingly, a fifth of all studies afflicted by COIs did not fully declare them at all. To prevent a harmful effect of COIs and IS on the internal validity of studies mediated by different types of bias, full transparency is ultimately required. This can only be achieved by detailed declaration of COIs/IS and comprehensive reporting of the research methodology and the corresponding results.

Authors' contribution

MS Wettstein: Protocol/project development, data collection or management, data analysis, manuscript writing/editing

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GS Kulkarni: Manuscript writing/editing

T Hermanns: Protocol/project development, manuscript writing/editing

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figure captions

Fig. 1 Flowchart visualizing the study selection process. *KTP: Potassium titanyl phosphate; LBO: Lithium triborate; NRCS: Non-randomized comparative study; PVP: Photoselective vaporization of the Prostate; RCT: randomized controlled trial;*

Fig. 2 Assessment of conflicts of interest (A, B) and industrial sponsorship (C, D) stratified by favourability of the study outcomes. *COI: Conflict of interest;*